STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 118158

TO: Devesh Khare
Location: REM-5C35/5C18
Art Unit: 1623
Wednesday, March 31, 2004

Case Serial Number: 09/925816

From: Mary Hale
Location: Biotech/Chem Library
Rem 1D86
Phone: 2-2507

Mary.Hale@uspto.gov

Search Notes

If you have any questions, please stop by or call me at the above number.

118158

Access DB#_____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's full Name: Devesh Khare Examiner #: 77931 Date: 03/30/2004

Art Unit: 1623 Phone Number 272-0653 Serial Number: 09/925,816

Mail Box: Remsen 5C18 and Bldg/Room Location: 5C35 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be search Include the elected species or structures, key words, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: See Bib Data Sheet on e-dan.

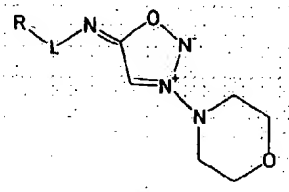
Inventors (please provide full names): See Bib Data Sheet on e-dan.

Earliest priority Filing Date: See Bib Data Sheet on e-dan.

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please carry out a search on the following claim:

1. A sugar-modified linsidomine (SIN-1) comprising a sugar moiety, a SIN-1 moiety and a glycosidic bond disposed between the sugar and SIN-1 moieties, said sugar-modified SIN-1 having the general structure



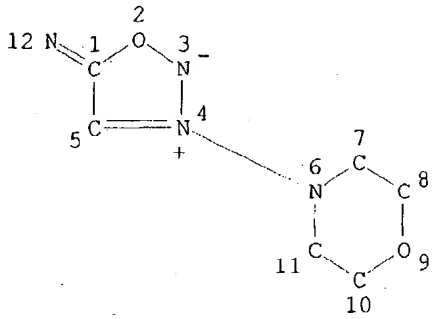
wherein L is a bond or a bifunctional linker group and wherein R is the sugar moiety and can comprise any carbohydrate.

Thank you

PTO-1590 (1-2000)

khare 09/925816

=> d l3 que stat;d 1-2 ide cbib abs
L1 STR



NODE ATTRIBUTES:
CHARGE IS *- AT 3
CHARGE IS *+ AT 4
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

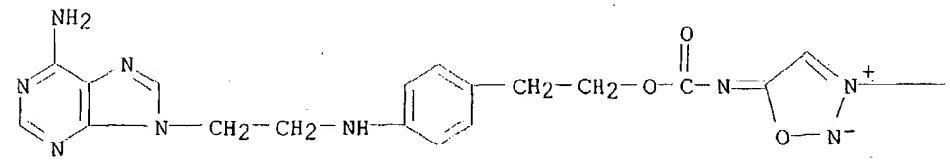
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L3 2 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 3 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

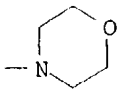
L3 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 625821-20-7 REGISTRY
CN 1,2,3-Oxadiazolium, 5-[[[2-[4-[[2-(6-amino-9H-purin-9-yl)ethyl]amino]phenyl]ethoxy]carbonyl]imino]-2,5-dihydro-3-(4-morpholinyl)-, inner salt (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C22 H26 N10 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT

PAGE 1-A



Searched by: Mary Hale 571-272-2507 REM 1D86

khare 09/925816

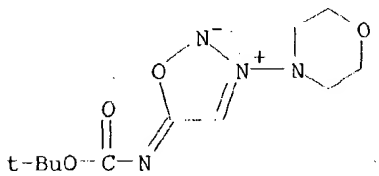


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:395871 Synthesis of sydnonimine derivatives as potential trypanocidal agents. Soulere, Laurent; Bringaud, Frederic; Hoffmann, Pascal (Laboratoire de Synthese et Physico-Chimie de Molecules d'Interet Biologique UMR CNRS 5068, Universite Paul Sabatier, Toulouse, 31062/4, Fr.). Journal of Heterocyclic Chemistry, 40(5), 943-947 (English) 2003. CODEN: JHTCAD. ISSN: 0022-152X. Publisher: HeteroCorporation.

AB N-(p-Nitrophenoxy)carbonyl-3-morpholino-sydnonimine (NCMS) has been prepared from 3-morpholinosydnonimine hydrochloride. Using the Griess assay and the superoxide-mediated reduction of ferricytochrome c, the nitric oxide (NO) and superoxide anion (O2-) - releasing properties in phosphate buffer pH 7.4 of this novel peroxynitrite donor was studied and compared with the known 3-morpholino-sydnonimine (SIN-1). From compound NCMS, a series of N-substituted sydnonimine derivs. were easily prepared that contain purine or melaminophenyl groups which specify a recognition by a trypanosomal purine transporter. The ability of these new sydnonimines to inhibit the uptake of [23H]adenosine on Trypanosoma equiperdum was studied.

L3 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 625821-17-2 REGISTRY
CN 1,2,3-Oxadiazolium, 5-[[(1,1-dimethylethoxy)carbonyl]imino]-2,5-dihydro-3-(4-morpholinyl)-, inner salt (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C11 H18 N4 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:395871 Synthesis of sydnonimine derivatives as potential trypanocidal agents. Soulere, Laurent; Bringaud, Frederic; Hoffmann, Pascal (Laboratoire de Synthese et Physico-Chimie de Molecules d'Interet Biologique UMR CNRS 5068, Universite Paul Sabatier, Toulouse, 31062/4, Fr.). Journal of Heterocyclic Chemistry, 40(5), 943-947 (English) 2003. CODEN: JHTCAD. ISSN: 0022-152X. Publisher: HeteroCorporation.

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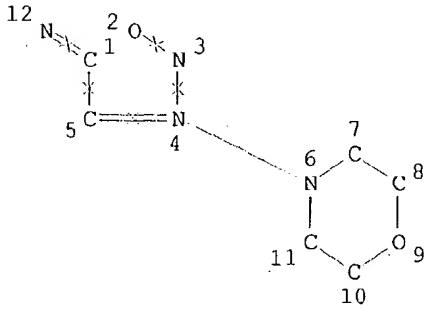
and superoxide anion (O2-) - releasing properties in phosphate buffer pH 7.4 of this novel peroxynitrite donor was studied and compared with the known 3-morpholino-sydnonimine (SIN-1). From compound NCMS, a series of N-substituted sydnonimine derivs. were easily prepared that contain purine or melaminophenyl groups which specify a recognition by a trypanosomal purine transporter. The ability of these new sydnonimines to inhibit the uptake of [23H]adenosine on Trypanosoma equiperdum was studied.

=> => d l6 que stat;s l6 not l3
L4 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
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SEARCH TIME: 00.00.01

L7 0 L6 NOT L3

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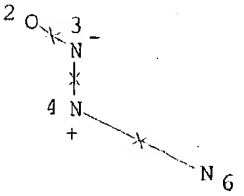
L8 STR



NODE ATTRIBUTES:
CHARGE IS *- AT 3
CHARGE IS *+ AT 4
DEFAULT MLEVEL IS ATOM

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khare 09/925816

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 4

STEREO ATTRIBUTES: NONE
L10 2 SEA FILE=REGISTRY SSS FUL L8

100.0% PROCESSED 17222 ITERATIONS 2 ANSWERS
SEARCH TIME: 00.00.01

L11 0 L10 NOT L3

=> fil medl,hcaplus,biosis,embase,wpids;s wang, p?/au,in or wang p?/au,in

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	482.62	482.83
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.32	-1.32

FILE 'MEDLINE' ENTERED AT 09:53:58 ON 31 MAR 2004

FILE 'HCAPLUS' ENTERED AT 09:53:58 ON 31 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE 'BIOSIS' ENTERED AT 09:53:58 ON 31 MAR 2004

FILE 'EMBASE' ENTERED AT 09:53:58 ON 31 MAR 2004

FILE 'WPIDS' ENTERED AT 09:53:58 ON 31 MAR 2004

'IN' IS NOT A VALID FIELD CODE
L12 2486 FILE MEDLINE
L13 6668 FILE HCAPLUS
L14 3161 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L15 2063 FILE EMBASE
L16 1032 FILE WPIDS

TOTAL FOR ALL FILES
L17 15410 WANG, P?/AU,IN OR WANG P?/AU,IN

=> s wu, x?/au,in or wu x?/au,in;s tang, x?/au,in or tang x?/au,in
'IN' IS NOT A VALID FIELD CODE
L18 2463 FILE MEDLINE
L19 10519 FILE HCAPLUS
L20 3230 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE

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L21        1818 FILE EMBASE
L22         996 FILE WPIDS

TOTAL FOR ALL FILES
L23       19026 WU, X?/AU,IN OR WU X?/AU,IN


'IN' IS NOT A VALID FIELD CODE
L24         932 FILE MEDLINE
L25        3834 FILE HCAPLUS
L26        1120 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L27         624 FILE EMBASE
L28         317 FILE WPIDS

TOTAL FOR ALL FILES
L29        6827 TANG, X?/AU,IN OR TANG X?/AU,IN

=> s l17 an dl23 and l29
MISSING OPERATOR L17 AN
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l17 and l23 and l29
L30           2 FILE MEDLINE
L31           5 FILE HCAPLUS
L32           3 FILE BIOSIS
L33           2 FILE EMBASE
L34           1 FILE WPIDS

TOTAL FOR ALL FILES
L35          13 L17 AND L23 AND L29

=> s l35 not 13
L36           2 FILE MEDLINE
L37           5 FILE HCAPLUS
L38           3 FILE BIOSIS
L39           2 FILE EMBASE

FILE 'WPIDS'
L34 MAY NOT BE USED HERE
The L-number entered was not created by a STRUCTURE or SCREEN command.

=> dup rem 135
PROCESSING COMPLETED FOR L35
L40           5 DUP REM L35 (8 DUPLICATES REMOVED)

=> d 1-5 cbib abs

L40  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
2003:203394   Document No. 138:226775  Preparation of morpholinosydnonimine-
     sugar conjugates as nitric oxide donors.  Wang, Peng George; Wu,
     Xuejun; Tang, Xiaoping (USA).  U.S. Pat. Appl. Publ. US 2003050256 A1
     20030313, 10 pp.  (English).  CODEN: USXXCO.  APPLICATION: US 2001-925816
     20010809.
AB   Sugar-modified SIN-1 compns. are provided.  The compns. are useful for
     generating NO in response to hydrolytic activity of a glycosidase specific
     for the O-glycosidic bond between the sugar and SIN-1 moieties.
     Pharmaceutical compns. containing the sugar-modified SIN-1 compns. and methods
     of using the compns. are also provided.  3-Morpholinosydnonimine-HCl was
```

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prepared by a standard method. To a solution of 4-nitrophenyl (2,3,4,6-tetra-O-acetyl-α/β-D-glucopyranosyl) carbonate in anhydrous pyridine was added the above compound The solvent was removed in vacuo to give a sticky oil and the residue was purified by silica gel column chromatog. to give a mixture of α- and β-anomers of the morpholinosydnonimine-glucose conjugate. The mixture was treated with NaOCH3 in anhydrous MeOH and Amberlyst-15 ion-exchange resin was added to neutralize the reaction mixture

L40 ANSWER 2 OF 5 MEDLINE on STN DUPLICATE 2
2002244817. PubMed ID: 11983528. Synthesis and cytotoxicities of mannose conjugated S-nitroso-N-acetylpenicillamine (SNAP). **Wu Xuejun; Tang Xiaoping;** Xian Ming; Brauschweiger Paul G; **Wang Peng George.** (Department of Chemistry, Wayne State University, Detroit, MI 48202, USA.) Bioorganic & medicinal chemistry, (2002 Jul) 10 (7) 2303-7. Journal code: 9413298. ISSN: 0968-0896. Pub. country: England: United Kingdom. Language: English.

AB A series of mannose conjugated S-nitroso-N-acetylpenicillamines (SNAPs) has been synthesized, and their cytotoxicities were assessed for DU 145 human prostate cancer cells and Hela R cancer cells.

L40 ANSWER 3 OF 5 MEDLINE on STN DUPLICATE 3
2002209362. PubMed ID: 11942788. Nitric oxide donors: chemical activities and biological applications. **Wang Peng George;** Xian Ming; **Tang Xiaoping; Wu Xuejun;** Wen Zhong; Cai Tingwei; Janczuk Adam J. (Department of Chemistry, Wayne State University, Detroit, Michigan 48202, USA.. pwang@chem.wayne.edu) . Chemical reviews, (2002 Apr) 102 (4) 1091-134. Ref: 798. Journal code: 2985134R. ISSN: 0009-2665. Pub. country: United States. Language: English.

L40 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
2001:372474 Document No. 135:195706 Glycosylated diazeniumdiolates: a novel class of enzyme-activated nitric oxide donors. **Wu, X.; Tang, X.;** Xian, M.; **Wang, P. G.** (Department of Chemistry, Wayne State University, Detroit, MI, 48202, USA). Tetrahedron Letters, 42(23), 3779-3782 (English) 2001. CODEN: TELEAY. ISSN: 0040-4039. OTHER SOURCES: CASREACT 135:195706. Publisher: Elsevier Science Ltd..

AB Synthetic procedures have been developed to attach the nitric oxide releasing diazeniumdiolate functional groups [N(O)NO]- to a carbohydrate unit. These glycosylated diazeniumdiolates exhibited significantly improved stability as compared to their parent diazeniumdiolate salts, yet they could readily release nitric oxide upon activation by glycosidases. Preliminary antitumor screen assay demonstrated that this class of compds. had antitumor activity.

L40 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
2001:639840 Enzyme activated NO donors: Glycosylated diazeniumdiolates. **Wang, Peng George; Wu, Xuejun; Tang, Xiaoping;** Xian, Ming (Department of Chemistry, Wayne State University, Detroit, MI, 48202, USA). Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001, MEDI-021. American Chemical Society: Washington, D. C. (English) 2001. CODEN: 69BUZP.

AB It is expected that sugar conjugated nitric oxide donors can be accumulated preferentially inside cells due to the expression of specific sugar transporters, and synthetic procedures are developed to attach the nitric oxide releasing diazeniumdiolate functional groups [N(O)NO]- to a carbohydrate unit. Three glycosylated diazeniumdiolates have been obtained by anchoring the pyrrolidinyl diazoniumdiolate anion to D-galactose, D-glucose and D-mannose. These glycosylated

diazeniumdiolates exhibited significantly improved stability as compared to their parent diazeniumdiolate salts, yet they could readily release nitric oxide upon activation by glycosidases. Preliminary antitumor screen assay demonstrated that this class of compds. had antitumor activity.

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=> fil reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    16.72     499.55

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -2.08      -3.40

FILE 'REGISTRY' ENTERED AT 09:55:04 ON 31 MAR 2004
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COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   30 MAR 2004  HIGHEST RN 669048-54-8
DICTIONARY FILE UPDATES:  30 MAR 2004  HIGHEST RN 669048-54-8

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> e linsidomine/cn 5
E1            1     LINSEED-OIL FATTY ACIDS, MALEATED/CN
E2            1     LINSEED-OIL MONO- GLYCERIDES/CN
E3            1 --> LINSIDOMINE/CN
E4            1     LINSIDOMINE CHLORHYDRATE/CN
E5            1     LINSIDOMINE HYDROCHLORIDE/CN

=> s ?linsidomine?/cns
L41           2 ?LINSIDOMINE?/CNS

=> e "sin-1"/cn
E1            1     SIN 3.0861/CN
E2            1     SIN 620/CN
E3            0 --> SIN-1/CN
E4            1     SIN20/CN
E5            1     SIN25/CN
E6            1     SIN3 ASSOCIATED POLYPEPTIDE (HUMAN CELL LINE PRIMARY CULTURE
                     GENE SAP18)/CN
E7            1     SIN3 ASSOCIATED POLYPEPTIDE P18 (HUMAN GENE SAP18)/CN
E8            1     SIN3 ASSOCIATED POLYPEPTIDE P18-LIKE PROTEIN (PLASMODIUM FAL
                    CIPARUM STRAIN 3D7 GENE MAL7P1.37)/CN
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Searched by: Mary Hale 571-272-2507 REM 1D86

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E9            1      SIN3-ASSOCIATED POLYPEPTIDE 18 (MOUSE STRAIN FVB/N CLONE MGC
                     :11444 IMAGE:3968600)/CN
E10           1      SIN3-ASSOCIATED POLYPEPTIDE, 18KD (HUMAN CLONE MGC:27131 IMA
                     GE:4794888)/CN
E11           1      SIN3-ASSOCIATED POLYPEPTIDE, 30KD (HUMAN CLONE MGC:13685 IMA
                     GE:4074154)/CN
E12           1      SIN3-ASSOCIATED-POLYPEPTIDE 18 (MOUSE STRAIN C57B/6 CLONE EM
                     EGR4)/CN

=> e sin 1?/cn
E1            2      SIN 10/CN
E2            1      SIN 10 (PHARMACEUTICAL)/CN
E3            0 --> SIN 1?/CN
E4            1      SIN 1A/CN
E5            1      SIN 1C/CN
E6            1      SIN 3/CN
E7            1      SIN 3.0861/CN
E8            1      SIN 620/CN
E9            1      SIN20/CN
E10           1      SIN25/CN
E11           1      SIN3 ASSOCIATED POLYPEPTIDE (HUMAN CELL LINE PRIMARY CULTURE
                      GENE SAP18)/CN
E12           1      SIN3 ASSOCIATED POLYPEPTIDE P18 (HUMAN GENE SAP18)/CN

=> e sin 1/cn 5
E1            1      SIMVOTIN/CN
E2            2      SIMX4 (STREPTOMYCES AVERMITILIS STRAIN MA-4680)/CN
E3            1 --> SIN 1/CN
E4            1      SIN 1.2056/CN
E5            2      SIN 10/CN

=> s e3
L42           1 "SIN 1"/CN

=> e glycosid?/cn 5
E1            1      GLYCOSARCOSTIN/CN
E2            1      GLYCOSE-N-ACETYLAMINOMANNURONIC ACID POLYMER/CN
E3            0 --> GLYCOSID?/CN
E4            1      GLYCOSIDASE/CN
E5            1      GLYCOSIDASE (AGROBACTERIUM TUMEFACIENS STRAIN C58 GENE ATU32
                     85)/CN

=> s ?glycosid?/cns
L43        2012 ?GLYCOSID?/CNS

=> fil medl,hcaplus,biosis,embase;s (141 or 142 or "sin 1" or linsidomine?) and
(143 or glycosid?)
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              14.97     514.52

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                 ENTRY    SESSION
CA SUBSCRIBER PRICE                               0.00      -3.40

FILE 'MEDLINE' ENTERED AT 09:57:12 ON 31 MAR 2004

FILE 'HCAPLUS' ENTERED AT 09:57:12 ON 31 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'BIOSIS' ENTERED AT 09:57:12 ON 31 MAR 2004

FILE 'EMBASE' ENTERED AT 09:57:12 ON 31 MAR 2004

L44 0 FILE MEDLINE
L45 7 FILE HCAPLUS
L46 2 FILE BIOSIS
L47 3 FILE EMBASE

TOTAL FOR ALL FILES
L48 12 (L41 OR L42 OR "SIN 1" OR LINSIDOMINE?) AND (L43 OR GLYCOSID?)

=> s l48 not l3
L49 0 FILE MEDLINE
L50 7 FILE HCAPLUS
L51 2 FILE BIOSIS
L52 3 FILE EMBASE

TOTAL FOR ALL FILES
L53 12 L48 NOT L3

=> s l53 not l35
L54 0 FILE MEDLINE
L55 6 FILE HCAPLUS
L56 2 FILE BIOSIS
L57 3 FILE EMBASE

TOTAL FOR ALL FILES
L58 11 L53 NOT L35

=> dup rme l58
ENTER REMOVE, IDENTIFY, ONLY, OR (?):end

=> dup rem l58
PROCESSING COMPLETED FOR L58
L59 10 DUP REM L58 (1 DUPLICATE REMOVED)

=> d 1-10 cbib abs

L59 ANSWER 1 OF 10 EMBASE
on STN
2002155357 EMBASE Nitric oxide induces the apoptosis of human BCR-ABL-positive myeloid leukemia cells: Evidence for the chelation of intracellular iron. Ferry-Dumazet H.; Mamani-Matsuda M.; Dupouy M.; Belloc F.; Thiolat D.; Marit G.; Arock M.; Reiffers J.; Mossalayi M.D.. M.D. Mossalayi, Bone Marrow Transplantation Lab., CNRS UMR5540, Universite de Bordeaux 2, 146 Rue Leo Saignat, 33076 Bordeaux Cedex, France. Leukemia 16/4 (708-715) 2002.
Refs: 44.
ISSN: 0887-6924. CODEN: LEUKED. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Anti-leukemia activity of human macrophages involves the generation of nitric oxide (NO) derivatives. However, leukemic transformation may involve mechanisms that rescue cells from NO-mediated apoptosis. In the present work, we analyzed the effects of exogenous NO on the proliferation

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of BCR-ABL(+) chronic myelogenous leukemia (CML) cells. As normal leukocytes, the proliferation of leukemia cells was inhibited by SNAP (S-nitroso-N-acetyl-penicillamine), GEA (Oxatriazolium aminochloride), and **SIN-1** (Morpholino-sydnonimine), whereas SNP (sodium nitroprusside) had no effect on leukemia cell growth. **SIN-1** induced higher anti-proliferation activity in BCR-ABL(+) cells, compared to normal hemopoietic cells. Inhibition of leukemia cell proliferation correlated with increased apoptosis and DEVDase activity. The simultaneous addition of exogenous iron reversed NO-mediated inhibition of cell growth, caspase activation and apoptosis in all BCR-ABL(+) cells tested. The quantification of intracellular iron levels in leukemia cells indicated that NO induced an early, dose-dependent decrease in ferric iron levels. Accordingly, elevation of intracellular iron protected leukemia cells from NO-mediated apoptosis. Together, the present work reveals the presence of an iron-dependant mechanism for leukemia cell rescue from NO-induced growth inhibition and apoptosis.

L59 ANSWER 2 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 1
2002:281540 Document No.: PREV200200281540. Influence of nitric oxide on the generation and repair of oxidative DNA damage in mammalian cells. Phoa, Nicole; Epe, Bernd [Reprint author]. Institute of Pharmacy, University of Mainz, Staudingerweg 5, D-55099, Mainz, Germany. epe@mail.uni-mainz.de. Carcinogenesis (Oxford), (March, 2002) Vol. 23, No. 3, pp. 469-475. print. CODEN: CRNGDP. ISSN: 0143-3334. Language: English.

AB We have analysed the effects of endogenously and exogenously generated nitric oxide (NO) in cultured mammalian fibroblasts on: (i) the steady-state (background) levels of oxidative DNA base modifications; (ii) the susceptibility of the cells to the induction of additional DNA damage and micronuclei by H2O2; and (iii) the repair kinetics of various types of DNA modifications. Steady-state levels of oxidative DNA base modifications, measured by means of an alkaline elution assay in combination with the repair endonuclease Fpg protein, were similar in NO-overproducing B6 mouse fibroblasts stably transfected with an inducible NO synthase (iNOS) and in control cells. Increased oxidative damage was only observed after exposure to high (toxic) concentrations of exogenous NO generated by decomposition of dipropylene-triamine-NONOate (DPTA-NONOate). Under these conditions, the spectrum of DNA modifications was similar to that induced by 3-morpholinosydnonimine, which generates peroxynitrite. The repair rate of additional oxidative DNA base modifications induced by photosensitization was not affected by the endogenous NO generation in the iNOS-transfected cells. However, it was completely blocked after pre-treatment with DPTA-NONOate at concentrations that did not cause oxidative DNA damage by themselves. In contrast, the repair of DNA single-strand breaks, sites of base loss (AP sites) and UVB-induced pyrimidine photodimers, was not affected. The endogenous generation of NO in the iNOS-transfected fibroblasts was associated with a protection from DNA single-strand break formation and micronuclei induction by H2O2. These results indicate that NO generates cellular DNA damage only inefficiently and can even protect from DNA damage by H2O2, but it selectively inhibits the repair of oxidative DNA base modifications.

L59 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
2001:509431 Document No.: PREV200100509431. The PARG inhibitor gallotannin decreases peroxynitrite- and hydrogen peroxide-induced astrocyte death by preventing NAD depletion. Ying, W. [Reprint author]; McGrue, Q. [Reprint author]; Swanson, R. A. [Reprint author]. Neurol, UCSF VAMC, San Francisco, CA, USA. Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 875. print.

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Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295. Language: English.

AB Excessive poly(ADP-ribose) polymerase 1 (PARP1) activation can mediate oxidative cell death and ischemic brain injury. Poly(ADP-ribose) glycohydrolase (PARG) is the enzyme responsible for degrading poly(ADP-ribose) polymers. We previously reported that the PARG inhibitors nobotanin and gallotannin (GT) can markedly decrease excitotoxic and oxidative neuronal death. In this study we reported that GT can also prevent cortical astrocyte death induced by the peroxynitrite generator **SIN-1** and the oxidant hydrogen peroxide. We also found that both GT and the PARP inhibitor benzamide can prevent hydrogen peroxide-induced NAD depletion of astrocytes. Because NAD depletion could be a key factor mediating PARP-induced cell death, the PARG inhibitor may block cell death by preventing NAD depletion. Additional studies showed that GT and benzamide did not produce additive effects in decreasing oxidative astrocyte death, suggesting PARG and PARP form a common cell death pathway.

L59 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

2000:102141 Document No. 132:218233 DNA damage in arsenite- and cadmium-treated bovine aortic endothelial cells. Liu, Fount; Jan, Kun-Yan (Institute of Zoology, Academia Sinica, Taipei, 11529, Taiwan). Free Radical Biology & Medicine, 28(1), 55-63 (English) 2000. CODEN: FRBMEH. ISSN: 0891-5849. Publisher: Elsevier Science Inc..

AB Reactive oxygen species have been shown to be involved in the mutagenicity, clastogenicity, and apoptosis of mammalian cells treated with arsenic or cadmium. As these endpoints require several hours of cellular processing, it is not clear that reactive oxygen species damage DNA directly or interfere with DNA replication and repair. Using single-cell alkaline electrophoresis, the authors have detected DNA strand breaks (DSBs) in bovine aortic endothelial cells by a 4-h treatment with sodium arsenite (As) and cadmium chloride (Cd) in sublethal concns. As-induced DSBs could be decreased by nitric oxide (NO) synthase inhibitors, superoxide scavengers, and peroxynitrite scavengers and could be increased by superoxide generators and NO generators. Treatment with As also increased nitrite production These results suggest that As-increased NO may react with O2·- to produce peroxynitrite and cause DNA damage. The results showing that Cd increased cellular H2O2 levels and that Cd-induced DSBs could be modulated by various oxidant modulators suggest that Cd may induce DSBs via O2·-, H2O2, and ·OH. Nevertheless, the DSBs in both As- and Cd-treated cells seem to come from the excision of oxidized bases such as formamidopyrimidine and 8-oxoguanine, as the Escherichia coli enzyme formamidopyrimidine-DNA glycosylase (Fpg) increased DSBs in cells treated with As, 3-morpholinosydnonimine (a peroxynitrite-generating agent), Cd, or H2O2.

L59 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN

1997:684486 Document No. 127:355946 Recombinant alphavirus-based vectors with reduced inhibition of cellular macromolecular synthesis. Dubensky, Thomas W., Jr.; Polo, John M.; Belli, Barbara A.; Schlesinger, Sondra; Dryga, Sergey A.; Frolov, Ilya (Chiron Viagene, Inc., USA; Washington University; Dubensky, Thomas W., Jr.; Polo, John M.; Belli, Barbara A.; Schlesinger, Sondra; Dryga, Sergey A.; Frolov, Ilya). PCT Int. Appl. WO 9738087 A2 19971016, 308 pp. DESIGNATED STATES: W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU,

MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2.
APPLICATION: WO 1997-US6010 19970404. PRIORITY: US 1996-628594 19960405; US 1996-668953 19960624; US 1996-679640 19960712.

AB Isolated nucleic acid mols. are disclosed, comprising an alphavirus nonstructural protein gene which, when operably incorporated into a recombinant alphavirus particle, eukaryotic layered vector initiation system, or RNA vector replicon, has a reduced level of vector-specific RNA synthesis, as compared to wild-type, and the same or greater level of proteins encoded by RNA transcribed from the viral junction region promoter, as compared to a wild-type recombinant alphavirus particle. Also disclosed are RNA vector replicons, alphavirus vector constructs, and eukaryotic layered vector initiation systems (ELVS) which contain the above-identified nucleic acid mols. Thus, a variant strain (**SIN-1**) of Sindbis virus (a pos. strand RNA virus) is provided which exhibits 10-fold reduced levels of viral-specific RNA in BHK cells, and for which the level of inhibition of host cell protein synthesis in **SIN-1** virus-infected cells is significantly lower compared to wild-type virus-infected cells. **SIN-1** is capable of establishing persistent infection in vertebrate cells, as compared to lytic, cytopathogenic wild-type strains of Sindbis virus. The **SIN-1** phenotype is mapped to the nonstructural genes, and specifically to a mutation within the Leu-Xaa-Pro-Gly-Gly motif of the nsp2 gene. **SIN-1** derived vector backbones are constructed and inserted into a plasmid DNA containing a bacteriophage RNA polymerase promoter, such that transcription in vitro produces an RNA mol. that acts as a self-replicating mol. (replicon) upon introduction into susceptible cells. The basic **SIN-1** RNA vector replicon is comprised of the following ordered elements: **SIN-1** nsp genes, subgenomic RNA promoter region, a polylinker sequence which may contain heterologous sequence insertions, the **SIN-1** 3'-nontranslated region, and a polyadenylate sequence. Following transfection into susceptible cells, autonomous replication of the RNA vector replicon occurs as for virus, and the heterologous sequences are synthesized as highly abundant subgenomic mRNA mols., which in turn serve as translational template for the heterologous gene product. Plasmid DNA-based alphavirus-derived expression vectors (ELVS) are also constructed; the ELVS plasmid DNA vector involves the conversion of a self-replicating vector RNA into a layered DNA-based expression system. Reporter protein expression vectors are constructed by inserting the lacZ, SEAP (secreted alkaline phosphatase), or luciferase reporter genes into the ELVS vector backbone. Modifications of the plasmid DNA **SIN-1**-derived expression vectors are also described involving the hepatitis B virus posttranscriptional regulatory element (PRE), the Mason-Pfizer monkey virus RNA-transporting constitutive transport element (CTE), and the RNA polymerase I promoter. Alphavirus packaging cell lines (PCL) are provided, whereby the virus-derived structural proteins necessary for RNA packaging and formation of recombinant alphavirus vector particles are encoded by one or more stably transformed structural protein expression cassette(s). The generation of alphavirus PCL, coupled with the construction of DNA-based alphavirus vectors, provides a straightforward mechanism to derive alphavirus vector producer cell lines. Finally, methods are described for the generation of alphavirus-derived empty or chimeric viral particles: e.g., a heterologous alphavirus glycoprotein DH cassette containing the capsid gene from Roos River virus and the glycoprotein genes from Sindbis virus.

L59 ANSWER 6 OF 10 EMBASE
on STN

96343351 EMBASE Document No.: 1996343351. DNA damage by peroxynitrite characterized with DNA repair enzymes. Epe B.; Ballmaier D.; Roussyn I.;

Briviba K.; Sies H.. Institut fur Pharmazie, Universitat Mainz, Staudinger Weg 5,D-55099 Mainz, Germany. Nucleic Acids Research 24/21 (4105-4110) 1996.
ISSN: 0305-1048. CODEN: NARHAD. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The DNA damage induced by peroxynitrite in isolated bacteriophage PM2 DNA was characterized by means of several repair enzymes with defined substrate specificities, Similar results were obtained with peroxynitrite itself and with 3-morpholinosydnonimine (**SIN-1**), a compound generating the precursors of peroxynitrite, nitric oxide and superoxide. A high number of base modifications sensitive to Fpg protein which, according to HPLC analysis, were mostly 8-hydroxyguanine residues, and half as many single-strand breaks were observed, while the numbers of oxidized pyrimidines (sensitive to endonuclease III) and of sites of base loss (sensitive to exonuclease III or T4 endonuclease V) were relatively low. This DNA damage profile caused by peroxynitrite is significantly different from that obtained with hydroxyl radicals or with singlet molecular oxygen. The effects of various radical scavengers and other additives (t-butanol, selenomethionine, selenocystine, desferrioxamine) were the same for single-strand breaks and Fpg-sensitive modifications and indicate that a single reactive intermediate but not peroxynitrite itself is responsible for the damage.

L59 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
1995:771773 Document No. 123:163910 Inhibition of ADP-ribose pyrophosphatase-I by nitric-oxide-generating systems: a mechanism linking nitric oxide to processes dependent on free ADP-ribose. Ribeiro, Joao Meireles; Cameselle, Jose Carlos; Fernandez, Ascension; Canales, Jose; Pinto, Rosa Maria; Costas, Maria Jesus (Dep. Bioquim. Biol. Mol. Genet., Univ. Extremadura, Badajoz, E-06080, Spain). Biochemical and Biophysical Research Communications, 213(3), 1075-81 (English) 1995. CODEN: BBRCA9. ISSN: 0006-291X. Publisher: Academic.

AB Rat liver ADP-ribose pyrophosphatase-I (ADPRibase-I; EC 3.6.1.13) hydrolyzes ADP-ribose with high specificity and a low Km. Thus it can participate in the control of free ADP-ribose and nonenzymic ADP-ribosylation of proteins. Here we show that ADPRibase-I was inactivated by acidified nitrite, whereas sodium nitroprusside (SNP) or 3-morpholinosydnonimine (**SIN-1**) at pH 7.5 produced a dose- and time-dependent Km increase from 0.5 μM to 2 μM. The effects of SNP and **SIN-1** depended on the presence and concentration of dithiothreitol, pointing to S-nitrosylation of enzyme thiols. It is suggested that, by inhibiting ADPRibase-I, NO can stimulate nonenzymic ADP-ribosylation of targets susceptible to micromolar free ADP-ribose. This is discussed in relation to apparently contradictory earlier reports on the role of NO in the ADP-ribosylation of actin.

L59 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
1993:119628 Document No. 118:119628 Nitric oxide perferentially stimulates auto-ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase compared to alcohol or lactate dehydrogenase. Dimmeler, Stefanie; Bruene, Bernhard (Fac. Biol., Univ. Konstanz, Konstanz, W-7750, Germany). FEBS Letters, 315(1), 21-4 (English) 1993. CODEN: FEBLAL. ISSN: 0014-5793.

AB Recently it was demonstrated that the radical nitric oxide (NO) stimulates the auto-ADP-ribosylation of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), resulting in enzyme inhibition. To further characterize this auto-ADP-ribosylation reaction, alc. dehydrogenase (ADH) and lactate dehydrogenase (LDH) were studied for comparison. Whereas auto-ADP-ribosylation of ADH was stimulated to a minor extent by the NO-liberating agent 3-morpholinosydnonimine (**SIN-1**), LDH was unaffected. The susceptibility of

dehydrogenases towards auto-ADP-ribosylation correlated with the potency of NO to decrease enzyme activity. Again, GAPDH was much more sensitive compared to ADH, whereas LDH again was unaffected. Interestingly, the efficiency of the SH-alkylating agent N-ethylmaleimide to inhibit the enzymic activity of the chosen dehydrogenases correlates with the sensitivity of dehydrogenases towards NO. These studies demonstrate the requirement of a reactive SH-group besides the NAD+ binding site as a prerequisite for NO-stimulated auto-ADP-ribosylation reactions. Furthermore, it was established that under physiol. conditions and among the dehydrognases tested, only GAPDH is a potential target for this post-translational protein modification mechanism.

L59 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
1992:587160 Document No. 117:187160 Nitric oxide causes ADP-ribosylation and inhibition of glyceraldehyde-3-phosphate dehydrogenase. Dimmeler, Stefanie; Lottspeich, Friedrich; Bruene, Bernhard (Fak. Biol., Univ. Konstanz, Konstanz, Germany). Journal of Biological Chemistry, 267(24), 16771-4 (English) 1992. CODEN: JBCHA3. ISSN: 0021-9258.

AB Nitric oxide and nitric oxide-generating agents like 3-morpholinosydnonimine (**SIN-1**) stimulate the mono-ADP-ribosylation of a cytosolic, 39-kDa protein in various tissues. This protein was purified from human platelet cytosol by conventional and fast-protein liquid chromatog. techniques. N-terminal sequence anal. identified the isolated protein as the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Nitric oxide stimulates the auto-ADP-ribosylation of GAPDH in a time and concentration-dependent manner with maximal effects after about 60 min. Associated with ADP-ribosylation is a loss of enzymic activity. The NAD+-free enzyme is not inhibited by **SIN-1**, indicating the absolute requirement of NAD+ as the substrate of the ADP-ribosylation reaction. Inhibition of the glycolytic enzyme GAPDH may be relevant as a cytotoxic effect of NO complementary to its inhibitory actions on iron-sulfur enzymes like aconitase and electron transport proteins of the respiratory chain.

L59 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
1992:527958 Document No. 117:127958 Nitric oxide stimulates the ADP-ribosylation of a 41-kDa cytosolic protein in Dictyostelium discoideum. Tao, Yongping; Howlett, Allyn; Klein, Claudette (Sch. Med., St. Louis Univ., St. Louis, MO, 63104, USA). Proceedings of the National Academy of Sciences of the United States of America, 89(13), 5902-6 (English) 1992. CODEN: PNASA6. ISSN: 0027-8424.

AB NO-releasing compds. activated an ADP-ribosyltransferase activity in the cytosol of D. discoideum. The enzyme ADP-ribosylated a cytosolic protein of .apprx.41 kDa, p41. Neither cGMP nor GTP and its analogs affected this ADP-ribosylation. Protein p41 differs from other substrates ADP-ribosylated by cholera, pertussis, or diphtheria toxins. Treatment of ADP-ribosylated p41 with snake venom phosphodiesterase released AMP, indicating a mono-ADP-ribose-protein linkage. This linkage was stable to neutral NH2OH, but was sensitive to Hg2+ and MeI, suggesting an attachment to a cysteine residue. Treatment of intact cells with NO-releasing compds. appeared to stimulate the ADP-ribosylation of p41 and this modification was reversible.

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